In re Application of: Lior GEPSTEIN et al
Serial No.: 10/759,734
Filed: January 20, 2004
Office Action Mailing Date: July 9, 2008

Examiner: Anoop Kumar Singh
Group Art Unit: 1632
Attorney Docket: 27395

REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested.

Claims 1-177, 182-186 and 196-199 are in this Application. Claims 1-175 and 182-185 have been withdrawn from consideration. Claims 176-177, 186 and 196-199 have been rejected.

35 U.S.C. § 102 Rejections

The Examiner has rejected claims 176-177, 186 and 196-199 under 35 U.S.C. § 102(e) as being anticipated by Funk et al. (US 6667176).

The Examiner states that Funk et al. teach an isolated a 4 day in-vitro suspension of EBs which is transferred to polyornithine-coated plates for additional 7 days to obtain beating cells exhibiting a cardiomyocyte phenotype.

The Examiner further states that the claimed and prior art products are identical or substantially identical or are produced by identical or substantially identical methods.

Applicant disagrees with the Examiner's assessment that Funk et al. teach isolated human embryoid bodies which include non-cystic embryoid bodies composed of cells having a cardiac phenotype simply because the culturing times reported by Funk et al. although capable of producing cardiomyocyte progenitors are incapable of producing non-cystic embryoid bodies which include such progenitors.

In Example 5 of US 6667176, Funk et al. teaches the following:

"The hES cells were dissociated into small clumps ..., and cultured in suspension to form embryoid bodies (EBs) ... After 4 days in suspension, the aggregates were transferred onto polyornithine-coated plates, and cultured for additional 7 days. The cultures were then examined for the presence of beating cells, and processed for immunohistochemistry." (emphasis added)

Thus, Funk et al. teaches a culturing period of 4 days in suspension and 7 days on poly-ornithine plates. As a result the EBs of Funk et al. were subjected to a differentiation period of 11 days since as is clearly stated by Funk et al., poly-ornithine coated plates induce, rather than suspend differentiation (Column 17, lines 9-16):

"Briefly, a suspension of undifferentiated pPS cells is prepared, and then plated onto a solid surface that promotes differentiation. Suitable substrates include glass or plastic surfaces that are adherent, for example, by coating with a polycationic substance, such as a polyamine or ***polyornithine****"* (emphasis added)

Funk et al. also state that "About 8 days after differentiation, beating regions were identified in all cultures" implying that 8 days following the 11 day period (4+7) of differentiation - 19 days in total, cardiomyocyte progenitors appeared in the EBs, which at this stage are cystic EBs as was explained in the previous response.

These time periods of culturing and appearance of cardiomyocyte progenitors correspond well to the time periods taught by the prior art cited in the previous office action; those prior art references were withdrawn following the previous response as being irrelevant to the claims pending in the application.

As was stated in the previous response, the EBs of the present invention were generated by culturing human embryonic stem cells for 7-10 days under non-adherent conditions and then transferring the formed EBs to gelatin-coated plates which froze the formed EBs in the morphological state achieved by the 7-10 days of culturing under non-adherent conditions. As was stated in the previous response, 7-10 days of culturing corresponds to a developmental stage which precedes the cystic (also termed vacuated) phase.

In addition, the Examiner states that Funk et al. generated EBs that include cardiomyocyte progenitors, however, it should noted that the markers used by Funk et al. (such as troponin) are not specific to cardiac muscle cells and that Funk et al. did not demonstrate that the cardiomyocyte progenitors of the EBs are capable of

differentiating into mature cardiomyocytes. In any case, the culturing approach of the present invention results in a vastly different culture of EBs both in general EB morphology (non-vacuated) and in the quantity and quality of cardiomyocyte progenitors included therein.

Thus, the methodology employed by the present invention as well as the EB culture formed thereby is clearly different from that of Funk et al. and as such, the present invention as claimed is neither anticipated nor rendered obvious by the teachings of Funk et al.

The Examiner has also rejected claims 176, 177, 186 and 196-199 under 35 USC 102(e) as being anticipated by Thomson et al. (US 7220584 - effective filing date Feb 21, 2000).

The Examiner states that Thomson et al. teach an in vitro culture of human EBs containing cells that differentiate to cardiac phenotype. The Examiner further states that Thomson teaches culturing of 11 days in suspension followed by mechanical or chemical dispersal and reattachment of dispersed cells to gelatin coated tissue culture plates.

As is clearly stated in US 7220584, the methodology of Thomson et al. is effected as follows:

"Following culture in suspension for up to 11 days, embryoid bodies are dispensed by mechanical or chemical means and can be allowed to reattach to tissue culture plates treated with gelatin or matrix, in ES medium. (emphasis added)

The above described approach results in:

Displaced, plated embryoid bodies will form flattened monolayers and can be maintained by replacing medium every 2 days." (emphasis added)

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Such monolayers no longer have EB morphology or physiology; differences between such monolayers and the EBs of the present invention are described in the Examples section of the instant application (see, Example 2 of the instant application). In addition, Thomson et al. state that generation of cell lineages of various origins requires additional culturing steps beyond the initial generation of EBs in suspension.

For example, cardiac lineage differentiation requires serum culturing steps and application of techniques described by Doetschman et al.:

"If cardiac lineages are desired one could use techniques analogous to T. Doetschman et al., 87 J. Embry. Exper. Morph. 27 45 (1985). One could plate the bodies in serum-containing medium with no additives".

Further evidence to the differences between the method of Thomson et al. and the present invention comes from an article published by Thomson and others in 2003 (He et al. enclosed herewith). In this article, the authors acknowledge the pioneering discoveries of the present inventors (see the first 4 lines of the introduction), clearly supporting the fact that earlier work published by Thomson, including US 7220584, is not similar in any way to the teachings of the present invention.

Thus, contrary to the Examiners Assertion, Thompson et al. do not describe or suggest non-vacuated EBs that include cardiomyocyte progenitors but merely provide methodology for producing EBs which can then be used as starting material for subsequent production of cardiomyocyte progenitors via additional culturing steps.

Therefore, in sharp contrast to the present invention, the method of Thomson et al. requires additional differentiation steps (following EB formation) in order to generate cardiac progenitors.

Thus, the teachings of Thomson et al. do not anticipate or render obvious (e.g. in combination with Carpenter and Igelmund) the present invention as claimed.

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In view of the above amendments and remarks it is respectfully submitted that claims 176, 177, 186 and 196-199 are now in condition for allowance. A prompt notice of allowance is respectfully and earnestly solicited.

Respectfully submitted,

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Date: October 7, 2008

Enclosures:

- Reference He et al.